INTRODUCTION

The U.S. Environmental Protection Agency (EPA) was established in 1970 in response to growing concerns over polluted air, unclean rivers, unsafe drinking water, endangered species, and careless waste disposal. EPA was given the responsibility for implementing a broad set of federal environmental laws, which have contributed in the intervening years to significant improvements in environmental quality. Currently, EPA has jurisdiction over more than a dozen statutes enacted to protect public health and the environment (e.g, the Safe Drinking Water Act; the Food Quality Protection Act, and the Clean Air Act).

EPA is both a regulatory and a scientific agency; it is one of only a few federal organizations that operates in this capacity. The environmental laws that form the legal basis for the EPA's regulatory activities also authorize its research efforts (e.g., the Food Quality Protection Act; Amendments to the Safe Drinking Water Act). It is this research that provides the foundation for scientifically defensible environmental policies, programs, and regulations. EPA research is housed chiefly in the Office of Research and Development (ORD).

EPA's Mission

Protect human health and safeguard the natural environment – air, water, land – upon which life depends.

EPA'S OFFICE OF RESEARCH AND DEVELOPMENT (ORD)

ORD is the principal research arm of EPA. Its role is to provide the critical science for environmental decision-making. Unlike much of EPA, ORD has no direct regulatory function- its responsibility is to inform the regulatory process. Through the development of technical information and scientific tools, ORD's research strengthens EPA's science base, providing its Program Offices and Regional Offices with sound scientific advice and information for use in developing and implementing tenable environmental policies, regulations, and practices. ORD now is comprised of 7 national Laboratories and Centers across the country and addresses issues related to the environment and human health.

Human health research at ORD addresses needs arising from the **Risk Assessment and Risk Management Paradigm** (Figure 1). Human health risk assessment involves a qualitative and quantitative characterization of the relationship between environmental exposures and effects observed in exposed individuals and populations. The National Research Council (1983) has described four primary steps in the process of risk assessment, i.e., hazard identification, dose-response assessment, exposure assessment, and risk characterization. Risk assessment is the primary scientific input to the risk management process, which involves the recognition of a potential new risk and development, selection, and implementation of EPA actions to address the risk. Risk management often considers a wide variety of other factors. The overall process of risk assessment and risk management is often referred to as the Risk Assessment-Risk Management Paradigm.

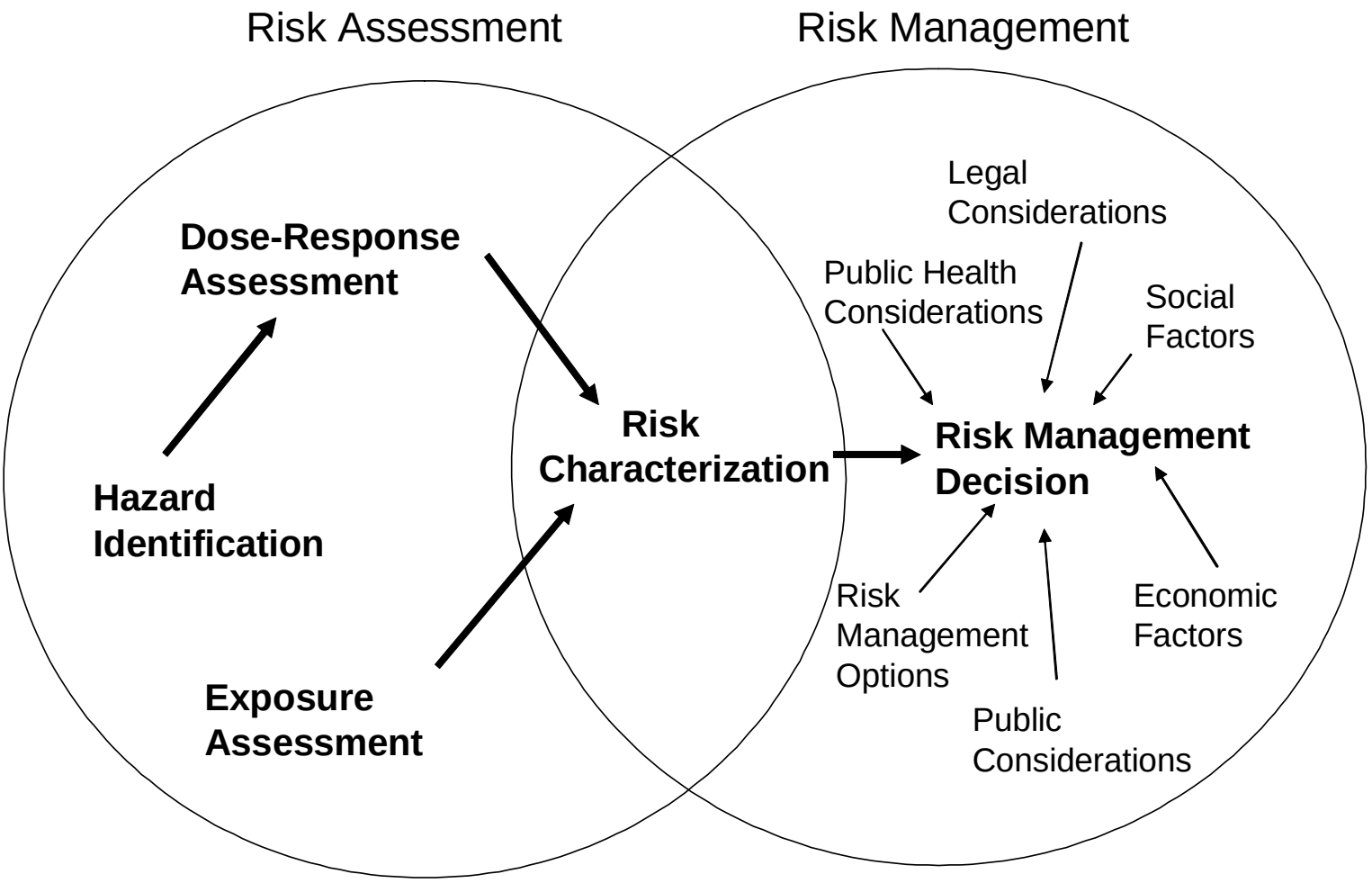


Figure 1 The Risk Assessment/Risk Management Paradigm

Until recently, ORD had aligned much of its organizational structure to be consistent with the Risk Assessment/Risk Management Paradigm (see text box). For example, the National Exposure Research Laboratory (NERL) focuses on measuring exposures and producing scientifically defensible exposure models that reduce the gaps in scientific knowledge related to actual human exposure to pollutants. In 1995, the EPA's Science Advisory Board (SAB) (US EPA, 1995) reviewed the state of exposure assessment science and reported that this area was hampered by a variety of technical limitations; that available exposure models had rarely been evaluated against actual human exposure measurements; there were no comprehensive human

Laboratories and Centers in ORD

Major Focus	Lab/Center
Hazard ID and Dose Response	NHEERL
Exposure and Dose Response	NERL
Risk Assessment	NCEA
Risk Management	NRMRL

exposure models that could describe the complex relationships between pollutant sources, environmental concentrations, exposure pathways, actual human exposures, and the dose that results from exposure to pollutants by multiple pathways; and that the methods available for both human exposure measurements and exposure modeling were too intrusive or costly to implement routinely.

In the Risk Assessment-Risk Management paradigm, dose-response assessment is the process for determining the likelihood of an adverse effect at a particular exposure or dose. A primary concern for dose-response assessment is an understanding of the dose of the environmental stressor that reaches its target organ, tissue, cell, or biomolecule. Research on issues related to dose is largely conducted at NERL and the National Health and Environmental Effects Research Laboratory (NHEERL). Research at NERL focuses on pharmacokinetic (PK) modeling to estimate internal dose metrics for multi-route aggregate exposure. Research at NHEERL focuses on determining the basis for improving inter- and intra-species extrapolations in risk assessment and determining the biologically effective dose of the parent compound or metabolite(s) of the pollutant. .

The goal of hazard identification is to describe and ultimately predict in humans the toxicological effects of environmental stressors that might occur due to exposure to environmental agents. Research related to hazard identification is largely conducted at NHEERL and focuses on test methods development and characterization of hazard potential in animal models. Clinical or epidemiological studies may also used to identify potential risks in the human population and generate testable hypothesis for future studies in animal or *in vitro* models. Risk assessment is often confounded by a number of uncertainties related to the risk assessment methodology, including extrapolation across species, extrapolation from short-term to lifetime exposures, and variability of response within the human population. A significant component of research at NHEERL focuses on reducing or eliminating those uncertainties. Research at NHEERL also seeks to understand the cascade of events between the presence of an environmental stressor at a target site and the ultimate manifestation of toxicity, i.e., the toxicity pathway. Knowledge of the sequence of biological events that must occur to produce an adverse effect (i.e., the mechanism of action, or an understanding of some, but not all, of the key biological steps leading to toxicity, i.e., the mode of action) is being used with increasing frequency in risk assessment.

The National Center for Environmental Assessment (NCEA) performs complex risk assessments of national interest and develops risk assessment methods, databases, and tools based on results produced by ORD and others. NCEA often serves an integrating function within ORD, bringing together results from hazard identification, dose-response assessment, and exposure assessment on issues related to the risk assessment process. The risk assessment program includes development of dose-response and exposure models, factors, databases and guidance for conducting risk assessment. Issues confronting the risk assessment program include how to use exposure, pharmacokinetic, and mechanistic data in risk assessment, harmonize cancer and non-cancer risk assessment methods, and conduct cumulative risk assessments of multiple pollutants. In 2004, NCEA was reorganized to focus on developing and providing guidance for risk assessments at the Agency.

The National Risk Management Research Laboratory (NRMRL) focuses on providing the most effective and useful risk management options and increasing better linkages between risk assessment and risk management efforts. Intramural research conducted by NERL, NHEERL, NCEA, and NRMRL is complemented by extramural research sponsored by ORD's National Center for Environmental Research (NCER). The Science to Achieve Results (STAR) program, which is administered by NCER, is the major extramural funding program within ORD. The STAR Program annually issues a series of competitive solicitations for

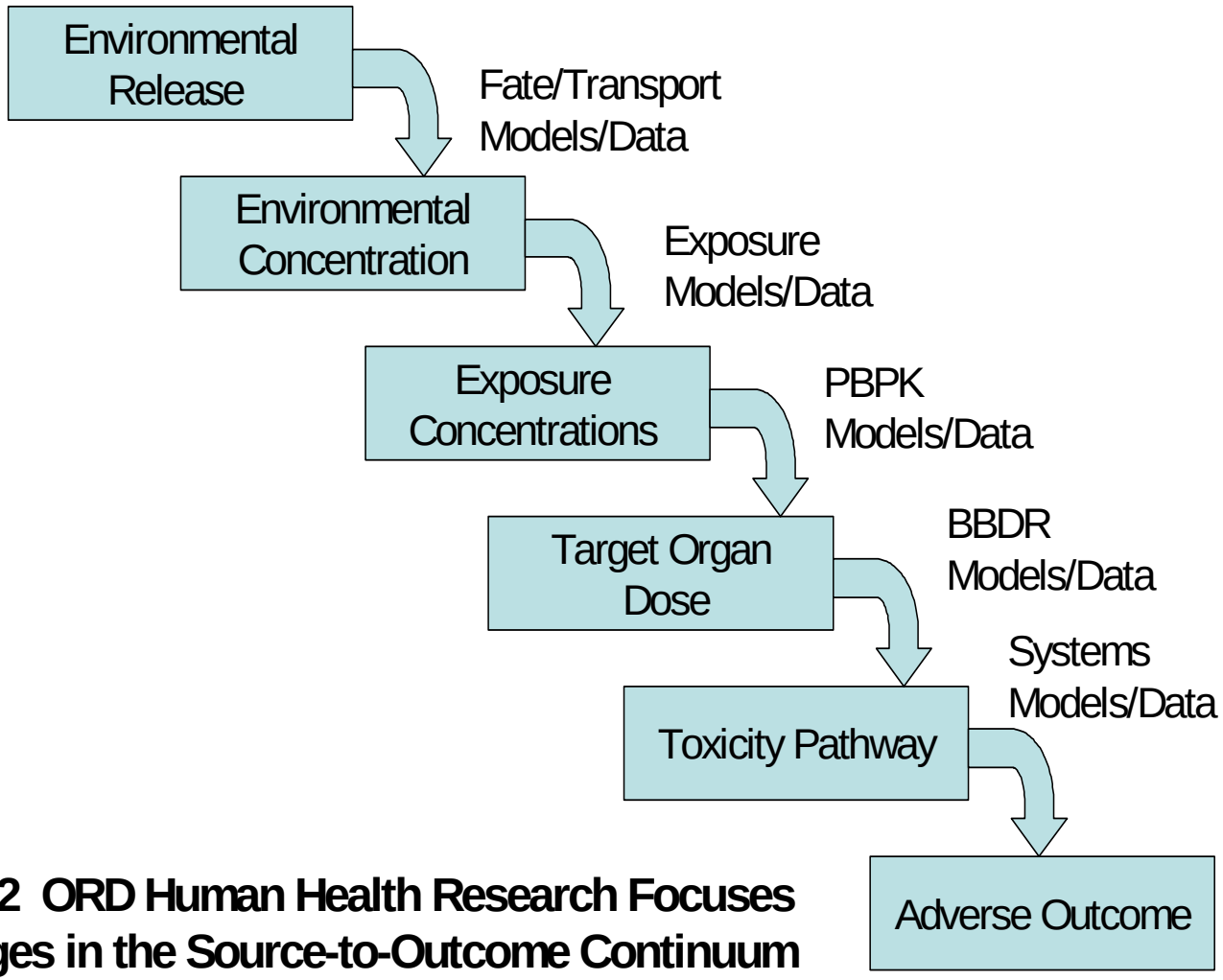


Figure 2 ORD Human Health Research Focuses on Linkages in the Source-to-Outcome Continuum

proposals from the scientific community to conduct research in areas of science important to EPA's mission. These solicitations are developed with significant cross-agency and interagency involvement in their planning, writing, and review and are often funded jointly with other Federal agencies such as the National Institute of Environmental Health Sciences (NIEHS). Proposals submitted to the STAR Program are subjected to both external review by non-competing scientists from outside of EPA and internal relevancy review conducted by scientists and managers from ORD and EPA's regulatory and regional offices. This review process ensures that only high quality projects of highest priority to EPA are supported through the STAR Program. The STAR Program communicates its research results to other scientists in ORD and EPA's program and regional offices and the public through websites, meetings, and publications. Examples of STAR research include 12 EPA/NIEHS-supported Centers for Children's Health and Disease Prevention Research and individual studies, such as the development of biomarkers for risk assessment in children. Additional details concerning the extramural grants program may be found in Attachment 1 of this Section. The STAR program received favorable review in a recent report from the National Academy of Sciences (NRC, 2003).

In response to emerging research needs, ORD has recently formed two new Centers. The National Homeland Security Research Center relies on risk assessment data and methodologies developed in ORD. The Computational Toxicology Center is expected to be an integral partner in understanding mechanism at the

cellular and molecular level. A poster explaining in greater detail the new Computational Toxicology Center will be presented.

Recognizing that organizational structure has in the past tended to limit the scope and impact of the research at EPA, the current emphasis in the Human Health Program is moving toward addressing integrated, multi-disciplinary research questions. As illustrated in Figure 2, EPA's Human Health Program now focuses on research to address linkages lying along a continuum from the source of an agent through exposure and dose to adverse outcome such as disease. One example of the need for an integrated program arises from opportunities and challenges associated with data in recent reports from the Centers for Disease Control and Prevention (CDC, 2001, 2003). The first publication provided an ongoing assessment of the US population's exposure to 27 environmental chemicals using biomonitoring. The second report provides biomonitoring exposure data for over 100 environmental chemicals for the US population divided into age, gender and race/ethnicity groups. The exposure information could help prioritize research on the relation between exposure and health effects and help identify population groups with unusually high exposure for health effects evaluation. Efforts will be needed to link biomonitoring data back to pathway and source to guide risk management interventions.

EPA's Strategic Goals

1. Clean Air and Global Change
2. Clean and Safe Water
3. Land Preservation and Restoration
4. Healthy Communities and Ecosystems
5. Compliance and Environmental Stewardship

FRAMEWORK FOR RESEARCH PLANNING AT THE EPA

The framework for organizing research within ORD is drawn from **EPA's Strategic Goals** (see text box) (US EPA, 2003a). These Goals identify the overall environmental results, such as Clean Air and Global Change, that EPA is working to attain. EPA uses these goals to systematize the way in which we prioritize, plan, and implement our research, report our research findings and products, and budget our programs. Each goal is linked to key environmental statutes such as the Food Quality Protection Act or the Clean Air Act. The human health research being highlighted in this review is covered in **Strategic Goal 4: Healthy Communities and Ecosystems**.

EPA brings together a variety of programs, tools, approaches and resources to develop a cross-media, cross-Agency, integrated research program in order to protect human health. The Human Health Research Program represents EPA's only comprehensive program to address the limitations in human health risk assessment. Scientists across the EPA and various stakeholders use measurement-derived databases, models, and methods developed through this research program to strengthen the scientific foundation for human health risk assessment (see discussion on Progress to Meet the Long-Term Goals in the following Overview).

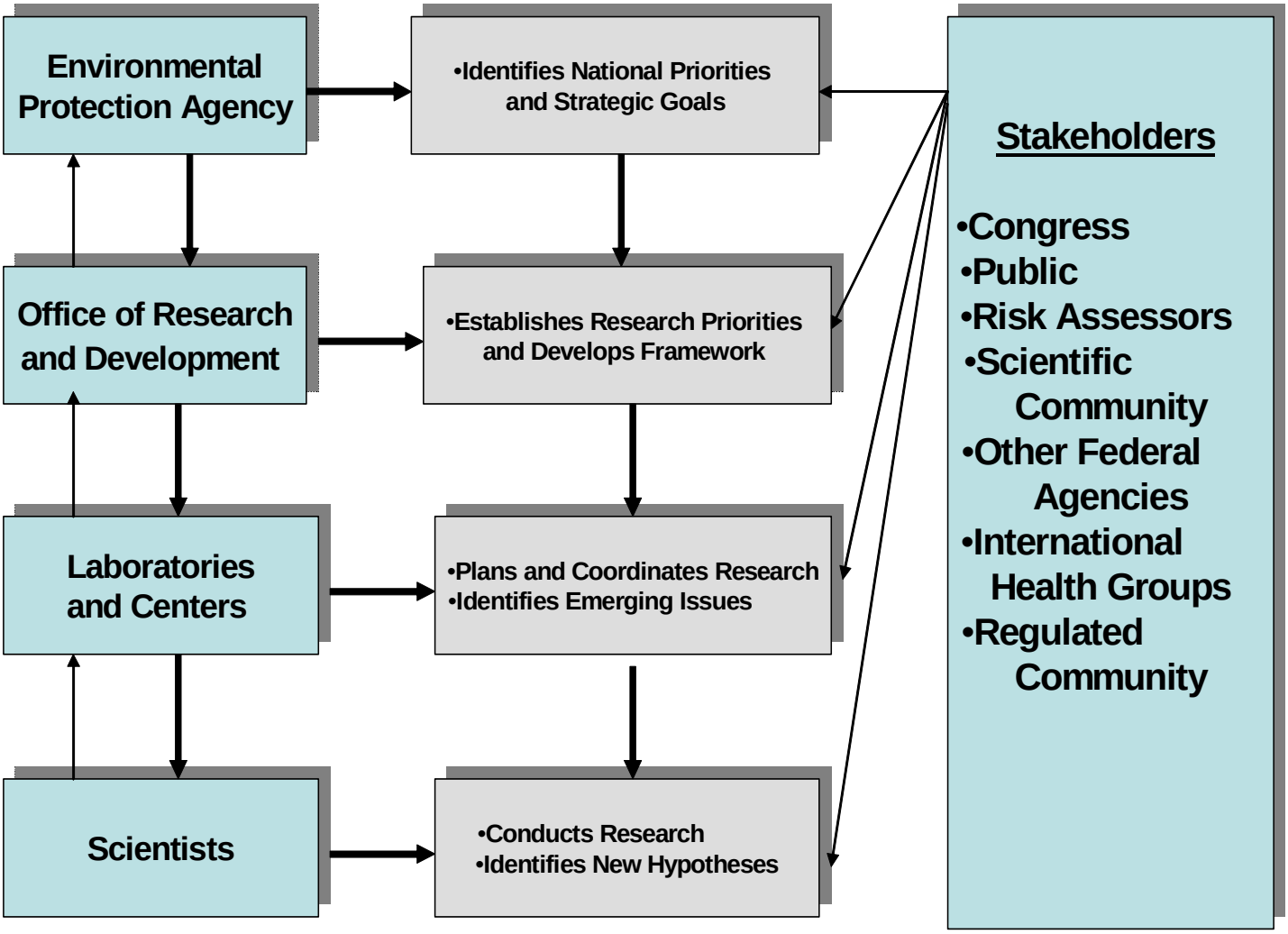


Figure 3 Research Planning at the Environmental Protection Agency

For each of the strategic goals in EPA's Strategic Plan, ORD's Laboratories and Centers have committed to reaching certain milestones and delivering specific products within a given time period, thus providing a mechanism for measuring tangible progress toward completion of long-term objectives. This explicit accountability grew out of the Government Performance and Results Act (GPRA) passed by Congress in 1993; consequently, these Agency goals are sometimes referred to as "GPRA Goals."

ORD's first Strategic Plan (US EPA, 1996) focused on a risk-based approach to decision-making for determining research priorities. Using this risk-based process, ORD identified eight areas of greatest potential risk to human health and the environment (see text box on next page). The selection of these high-priority research topics was conducted in partnership with ORD's many stakeholders, including the external scientific community (EPA's Science Advisory Board, the National Research Council, other government agencies, and the private sector) and the Agency's Program and Regional Offices and scientific staff.

EPA's research agenda is determined by means of a research planning process involving every organizational level within the Agency. Figure 3 is a simplified diagram of the inter-relationships that exist

in research planning. All levels of EPA are influenced by a variety of stakeholders, which results in a process of identifying national health and environmental priorities and strategic goals. These are articulated in EPA's Strategic Plans, which are revised approximately every 5 years (US EPA, 2003a). These Plans focus on both organizational issues and research. Strategic Plans are broad in scope, articulating EPA's mission and its national environmental goals. Based on the strategic goals laid out in the ORD Strategic Plan, ORD establishes research priorities and develops a framework for addressing the strategic goals. These priorities are described in specific Research Strategies such as the *Human Health Research Strategy* (US EPA, 2003b), which was peer-reviewed by the SAB in 2002. . Research strategies provide the context for developing implementation plans at the Laboratory or Center level.

ORD's High Priority Research Areas

- Particulate Matter
- Drinking Water
- Clean Water
- Global Change
- Ecological Risk Assessment
- Human Health Risk Assessment
- Endocrine Disruptors
- Pollution Prevention and New Technologies

ORD Multi-Year Plans, in contrast, are more detailed, specifying the research approaches to be applied to the problems and integrating research across ORD. These Plans are developed with input from all of ORD's Laboratories and Centers and their staff play a lead role in their development. ORD's Multi-Year Plan for Human Health Research is available on the Internet at http://www.epa.gov/osp/myp.htm. The next version of the Human Health Multi-Year Plan will incorporate comments from the review by the Board of Scientific Councilors and an upcoming review by the Office of Management and Budget in 2005.

ORD Annual Research Planning also takes place within the Agency as part of the federally-mandated planning and budgeting process. Annual planning in ORD is driven largely by the commitments laid out in the process described above, but in addition, pressing needs may be identified by the Program and Regional Offices and ORD's scientific staff. These needs are then prioritized by Agency-wide teams (called Research Coordination Teams). Special attention is paid to research required to fulfill a legislative mandate, court order, or Agency GPRA commitment; priority setting also takes into consideration scientific feasibility, the status of ongoing research, budgetary constraints, and ORD's ability to make a contribution relative to other research institutions that may be working in the same area. The objective is to focus on environmental problems that pose the greatest risks to people and the environment (using criteria such as severity, permanence, scale), on uncertainties in risk assessment that can be effectively reduced, and on areas that clearly help the Agency fulfill its regulatory mandates. These research needs become the priorities for ORD.

While the problems ORD is tasked to solve are defined by the above process, the research agenda for solving these problems is determined by the Laboratories and Centers. ORD structures a coherent research program around the problem areas, with its various Labs and Centers playing specified roles. The Laboratories and Centers are held accountable for implementing research activities within the program and for addressing the priorities established through the ORD planning process. Scientists identify the critical paths for research to resolve the key scientific questions and are often the first to raise new questions and recommend new methods for problem-solving. Their suggestions and ideas are fed back into the planning process by several means, the most common being discussions with the ORD science management.

CORE AND PROBLEM-DRIVEN RESEARCH

Because EPA is a regulatory agency, it is recognized that research must be results-oriented and

customer- focused. Some research is required by law, while other research is initiated in response to specific environmental exigencies or opportunities. In the report *Building a Foundation for Sound Environmental Decisions,* however, the National Research Council (1997) recommended that EPA maintain a balanced program of **Core** and **Problem-Driven** research.

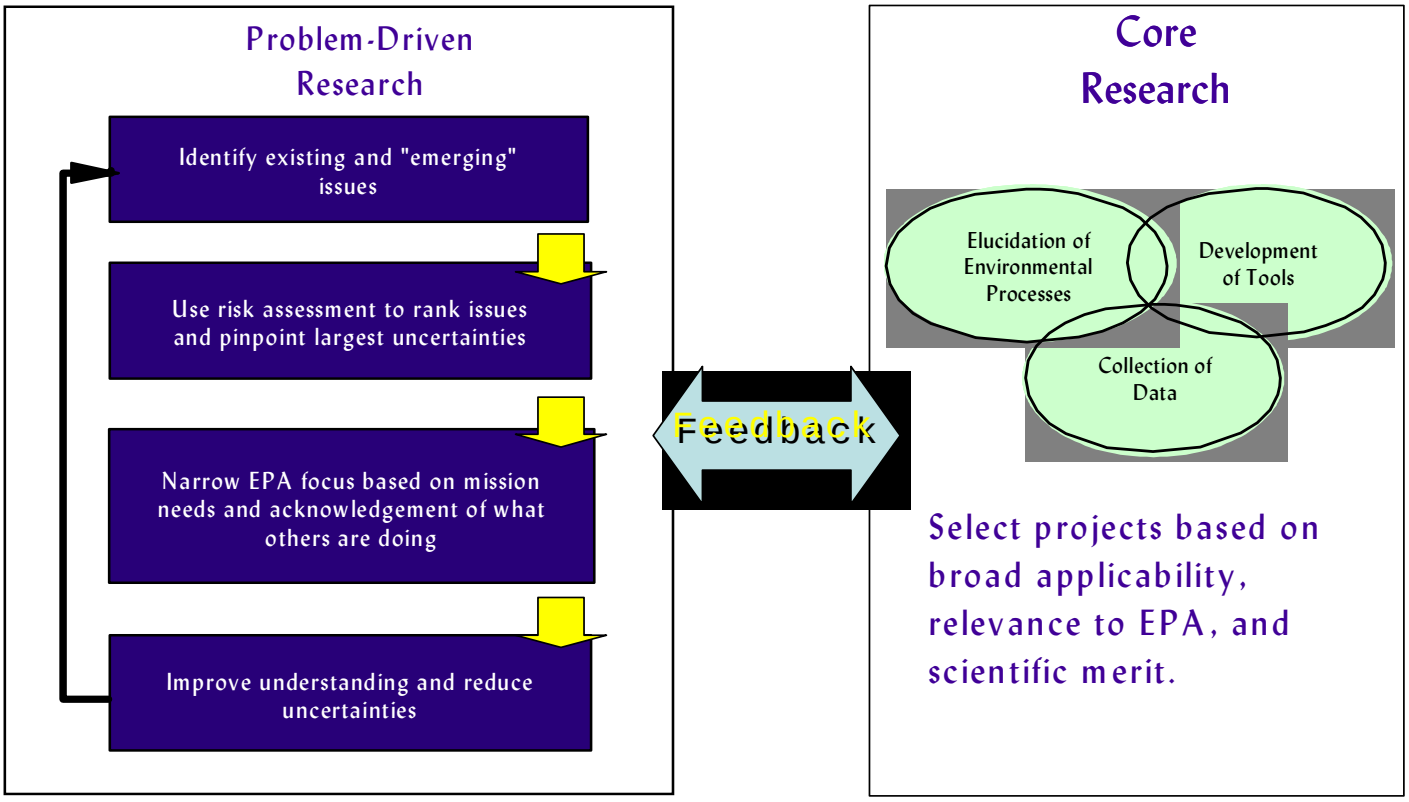
Core research seeks to produce a fundamental understanding of the key biological, chemical, and physical processes that underlie environmental systems, thus forging basic scientific capabilities that can be applied to a wide range of environmental problems. Core research addresses questions common to many EPA programs and they provide the methods and models needed to confront unforeseen environmental problems. Much of the Human Health Research Program can be categorized as core research since much of it focuses on multi-disciplinary cross-cutting issues such as susceptibility and extrapolation. **Problem-driven research**, on the other hand, focuses on regulatory or program activities, such as court-ordered deadlines. Problem-driven human health issues associated with specific pollutants (e.g., particulate matter, drinking water contaminants, air toxics, endocrine disruptors, pesticides and toxic substances) are addressed in separate ORD Research Strategies (http://www.epa.gov/ord/htm/researchstrategies.htm) and Multi-Year Plans (http://www.epa.gov/osp/myp.htm). The relative emphasis on research themes may change as ORD priorities shift, as new data surfaces, as court-ordered deadlines are met, or as budgets fluctuate. Substantial efforts are made by ORD, however, to build and maintain a research program that is both relevant to the scientific problem and responsive to EPA's needs.

As seen in Figure 4, core and problem-driven research are not mutually exclusive. In fact, they are highly complementary and interactive, each informing the other. Fundamental research issues that cut across several areas must often be addressed before more problem-driven questions can be studied. There is a constant need to integrate problem-driven and core research. For example, the Food Quality Protection Act of 1996 specifies that the EPA shall consider the risk associated with cumulative exposures of chemicals based on their mode of action. In order to develop predictive models of chemical interaction, fundamental research has to be done to identify the biological mode or mechanism of action to be used in the cumulative risk assessment. A component of ORD's Human Health Research Program focuses on developing mechanistic information on major classes of environmental stressors which can be used to develop predictive models for risk assessment. Another example of the need to link core and problem-driven research is that risk assessors are required to account for the unique susceptibilities of sensitive subpopulations in the risk assessment process. In this regard, part of ORD's Human Health Research Program focuses on identifying potential populations at risk and determining the extent to which their differential response to pollutants could influence the risk assessment process. The blend of core and problem-driven research yields a robust research portfolio that couples a stable core effort with research needs derived from the regulatory mission of the EPA.

SCIENCE LEADERSHIP AT EPA

ORD provides vital leadership in the environmental research arena, and its scientists are active in the scientific community at many levels. Within the EPA, we help shape the research agenda by contributing to research planning and coordination exercises, and we participate in the development of ORD Research Plans and Strategies. Our scientists represent the EPA on workshops and task forces addressing major risk assessment, public health, and environmental issues. Outside EPA, we influence the direction and priorities o f

Figure 4 Relationship Between Core and Problem-Driven Research



environmental research worldwide. We steer collaborative research efforts at the national and international level, we are members of international planning committees and research review panels, we serve on advisory boards of other major agencies and organizations, and we serve as adjunct faculty members at major universities across the nation. Examples of how ORD human health researchers have provided science leadership inside and outside the Agency are discussed in greater detail in the following Overview Section.

SCIENTIFIC ADVICE AND TECHNICAL ASSISTANCE

As part of our mission, ORD responds to diverse requests for scientific advice and technical consultation, both within and outside EPA. We provide technical support to the EPA advising its Program Offices and Regional Offices on scientific matters, by participating on Inter and Intra-Agency workgroups, and by helping to develop testing and risk assessment guidelines. We bring our expertise to bear at the national and international level by organizing scientific workgroups and symposia, and by serving in professional and scientific societies and on publication boards. We provide guidance to local, state, tribal, and international governments and other federal agencies, informing them on issues of environmental importance and enabling them to implement more effective environmental programs. We work to establish partnerships with the corporate, public, private, and educational sectors and assist them in setting and achieving environmental goals. We provide technical training and developmental opportunities for the senior scientist as well as the post doctoral candidate and the student. By sharing our skills and knowledge, we enhance the ability of other

organizations to protect public health and the environment, and we serve as an important catalyst for scientific and technological progress. How ORD human health researchers have provided scientific advice and technical assistance to the Agency is discussed in greater detail in the following Overview Section.

SUMMARY

The overall goal of the Human Health Research Program is to provide fundamental understanding of the physical and biological processes that underlie environmental systems and human populations at risk. It is expected that the products of this program will enable risk assessors and risk managers to reduce uncertainty in the risk assessments. The Overview Section that follows this Introduction discusses in greater detail the four criteria to be used to evaluate the Human Health Research Program, i.e., relevance, quality, performance and scientific leadership. The narrative on Relevance provides an overall conceptual framework for human health research, a discussion on how research priorities are developed at EPA, the interplay between core and problem-driven research, and examples of coordination with other stakeholders. The discussion of Quality focuses on how the products of the intramural and extramural research program are evaluated by peer-review and the allocation of resources to high priority research themes identified by the Agency's planning process. Performance discusses the Human Health Program within the context of the Human Health Multi-Year Plan and provides examples of how the program has made progress to meet the long-term goals of that plan. The narrative on Scientific Leadership provides specific examples of how human health researchers at EPA have contributed to advancing the state-of-the science in this disciplines related to priority research questions. Sections that follow the Overview include a discussion of each of the four main themes of the human health research (i.e., use of mechanistic data in risk assessment; aggregate/cumulative risk, protecting susceptible populations, and evaluation of public health outcomes). Following the narrative for each theme are abstracts describing each poster to be presented within that theme.

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